SUPPLEMENTARY METHODS

VOHF intervention

The VOHF study was carried out in the Hospital Universitari Sant Joan de Reus, (Spain). The study design and characteristics of the volunteers have been described in detail elsewhere.[30] Briefly, 12 healthy volunteers (six men and six women) between 22 and 60 years were recruited. The study was a postprandial, randomized, controlled, crossover trial consisting of the intake of 30 mL of the functional EVOOs after 12 hours of fasting. Blood samples were collected at 1, 2, 4 and 6 hours after the ingestion. Three intervention periods were included with three polyphenols-enriched EVOOs differing in phenolic content: L-EVOO (250 mg total phenols/kg of oil), M-EVOO (500 mg total phenols/kg of oil) and H-EVOO (750 mg total phenols/kg of oil). A EVOO with low phenolic content (80 mg total phenols/kg of oil) was used as enrichment matrix and the 3 oils were prepared by the addition of an extract obtained from freeze-dried olive cake rich in polyphenols.[30] Before each intervention period, a one-week washout period was carried out.[30] Phenolic composition of each functional EVOO is shown in **Supplementary Table 1**.

RT-PCR conditions and quality controls

MicroRNA levels were analyzed by Real-Time quantitative PCR (RT-qPCR). Isolated microRNAs were retro-transcribed with the TaqMan® MicroRNA Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, MA, USA). Before retrotranscription, 5fmol of single-strand cel-miR-54 was added to control for retrotranscription variability. 5 µl of RNA were used as a template. Resulting cDNA was pre-amplified with the TaqMan® PreAmp Master Mix (Thermo Fisher Scientific, Waltham, MA, USA). The pre-amplification product was diluted 1:20 and 3 µl of the diluted pre-amplification product was amplified by RT-qPCR with TaqMan OpenArray PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA) in a TaqMan custom OpenArray loaded using an OpenArray® AccuFill™ System (Thermo

Fisher Scientific, Waltham, MA, USA). The RT-qPCR was run in a QuantStudio™ 12K Flex Real-Time PCR System with OpenArray® Block (Thermo Fisher Scientific, Waltham, MA, USA). The fold-change (FC) in circulating microRNAs levels was measured as relative quantification using the $2^{-\Delta\Delta Ct}$ method comparing each time-point to basal point and was Log_2 transformed. The NormFinder algorithm[33] was used to select the best two endogenous reference microRNAs in each case. The best two endogenous microRNAs for normalization selected by NormFinder were: miR-192-5p and miR-221-3p for L-EVOO; miR-221-3p and miR-320a-3p for M-EVOO and miR-223-3p and miR-92a-3p for H-EVOO. The quadratic average of the two endogenous controls plus the exogenous cel-miR-54 control was used for normalization. The efficiency of all probes was assessed with a calibration curve using a control RNA from plasma. All microRNAs with an efficiency below 80% were discarded. Two non-template controls (NTC) were included in each plate, and all microRNAs with CTs over the NTC were also discarded. RT-qPCR was made in duplicate, and all microRNAs with >10% of inconsistent technical replicates were discarded.

In silico functional analyses settings

MicroRNAs significantly modified in, at least, one time-point in each treatment were selected for further functional analyses. Enrichment analysis was carried out with DIANA miRPath v0.3[34] to identify pathways regulated by modified microRNAs. We also searched for experimentally validated and predicted targets of these microRNAs using the miRWalk tool.[31] Predicted targets were analyzed with miRWalk comparing 8 algorithms (miRanda, TargetScan, miRDB, PITA, MicroT4, miRMap, microRNAMap and miRWalk) using stringent criteria in all of them. Predicted targets by, at least, 7 algorithms were selected for further analysis. Both, experimental and predicted targets, were analyzed for functional GO annotation terms, KEGG pathways enrichment and protein-protein interaction using Babelomics 5 and Software String.[35, 36]